CLAIMS

1. A process for in situ preparation of a chiral compound from an oxazaborolidine-borane complex, comprising the following steps:

1) adding to a suspension of a metal borohydride defined by formula (I):

$$MBH_4 \qquad (I)$$

in which:

M a metal ion is selected from the group consisting of sodium, potassium, lithium, and zinc:

a) a Lewis base of general formula (II) below:

$$R_1\text{–}A\text{–}(R_2)_n \qquad (II)$$

in which:

R_1 and R_2, which are identical or different, are selected from the group consisting of a hydrogen atom, an optionally substituted, linear alkyl, an optionally substituted branched alkyl, an optionally substituted aryl, an alkylaryl, a C_4-C_7 cycloalkyl, and R_1 and R_2 can together form a C_1-C_7 alkyl chain or an optionally substituted C_2-C_7 carbocycle;

n is equal to 1 or 2; and

A is an atom selected from the group consisting of a nitrogen, oxygen, sulfur and phosphorus; and

b) an inorganic acid ester of general formula (III) below:

$$R_3\text{–}X \qquad (III)$$

in which:

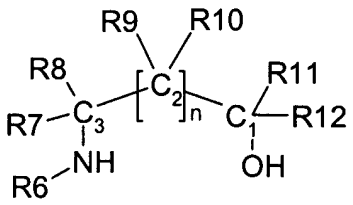
X is selected from the group consisting of a sulfonyloxy ester group ($-OS(O)_2OR_4$), a sulfonate ($-OS(O)R_5$) and a sulfite ($-OS(O)OR_5$); and

R_3, R_4 and R_5, which are identical or different, are selected from the group

consisting of a linear or branched alkyl, said alkyl being optionally substituted by a substituent selected from the group consisting of a halogen atom, an aryl, a heterocycle, a heteroaryl, an alkoxy group, an alkylthio group, an alkylaryl group a C_4-C_7 cycloalkyl, and

R_4 and R_5 together are selected from a C_1-C_7 alkyl chain and an optionally substituted C_1-C_7 carbocycle;

2) and then, adding to the product obtained after step 1 an optically active amino alcohol of general formula (IV) below:



(IV)

in which:

R_6 is selected from the group consisting of a hydrogen atom, a linear or branched C_{1-8} lower alkyl group; a C_{1-15} arylalkyl group, and a C_{1-15} arylalkyl group substituted by a substituent selected from the group consisting of C1-C5 alkyl and C_{1-5} alkoxy;

R_7, R_8, R_9, R_{10}, R_{11} and R_{12}, which are identical or different, independently are selected from the group consisting of a hydrogen atom, a C_{1-8} lower alkyl group, , a C_{6-12} aryl group, an aryl group substituted by a C_{1-5} alkyl; a C_{7-12} arylalkyl group, an arylalkyl group substituted by a C_{1-5} alkyl, with the proviso that R_6 and R_7 are different;

R_6 and R_7, or R_7 and R_{11}, or R_8 and R_9, or R_{10} and R_{11} together can form a C_{3-6} lower alkylene group, a substituted C_{3-6} lower alkylene group, R_8 and R_9 together can form an alkylene group that is optionally substituted or fused with a benzene ring,;

n is equal to 0, 1 , 2 or 3; and

at least one of C_1, C_2 and C_3 is an asymmetric carbon atom,

thereby obtaining said chiral compound.

2. The process of claim 1, wherein said compound of formula (II) is a linear or cyclic ether; a secondary or tertiary; a linear or cyclic thioether; an amino ether.

3. The process of claim 1, wherein said compound of formula (III) is selected from the group consisting of a dialkyl sulfate, a sulfuric acid bisaryloxyalkyl ester, a bisalkoxysulfonyloxyalkane, a dioxathiolane dioxide and dimethyl sulfate .

4. The process of claim 1, wherein, the amounts of Lewis base and inorganic ester are ranging between 1 and 2 equivalents, based on the metal borohydride.

5. The process of claim 1, wherein the compounds (I), (II) and (III) are brought into contact in step 1) in any order at a temperature ranging between 0°C and 75°C and the resulting reaction medium is stirred at room temperature for a period of time ranging between 0.5 and 4 hours.

6. The process of claim 1, further comprising adding, in step 2) to the product obtained after step 1):

a halide defined by formula (X):

$$M_1\text{–}Y \quad (X)$$

in which:

M_1 is selected from a sodium ion , a potassium ion, a lithium ion, an ammonium group and a phosphonium group; and

Y is a halogen atom selected from chlorine, bromine, fluorine and iodine;

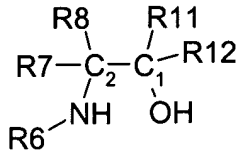
and then the optically active amino alcohol of formula (IV).

7. The process of claim 6, wherein M_1 is an ammonium group selected from the group consisting of tetraalkylammonium, pyridinium, alkylpiperidinium, alkyl-piperazinium, alkylpyrrolidinium and tetraalkylanilinium

8. The process of claim 6, wherein M_1 is a phosphonium group selected from arylphosphonium and alkylarylphosphonium.

9. The process of claim 6, wherein the halide of formula (X) is lithium chloride.

10. The process of claim 1, wherein n is equal to zero in formula (IV) which is of general formula (IVa):



(IVa)

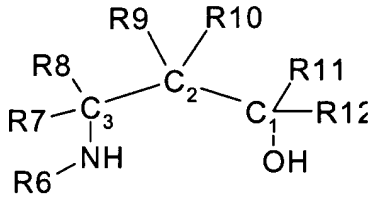
in which:

R_6, R_7, R_8, R_{11} and R_{12}, are as previously defined; and

At least one of C_1 and C_2 is an asymmetric carbon atom.

11. The process of claim 10, wherein said optically active product of formula (IVa) is (S)- or (R)-β,β-diphenyl-2-pyrrolidinylmethanol.

12. The process of claim 1, wherein n is equal to 1 in formula (IV) which is of general formula (IVb):



(IVb)

in which:

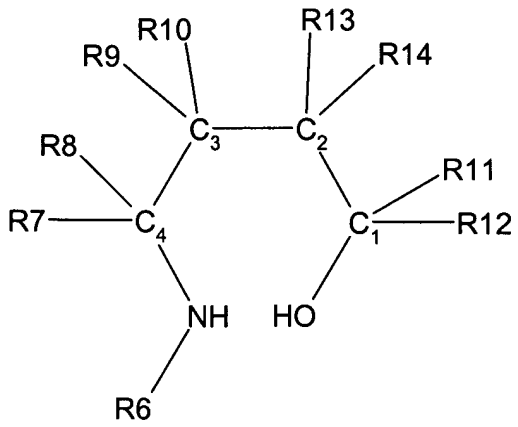
R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12},are as previously defined

At least one of C_1, C_2 and C_3 is an asymmetric carbon atom.

13. The process of claim 12, wherein said optically active product of formula (IVb) is selected from(S)- or (R)-β,β-diphenyl-2-pyrrolidinylethanol; (S)- or (R)-β,β-di(t-butyl)-2-piperidinylethanol ; and (S)- or (R)-2-phenyl-4-hydroxy-

piperidine.

14. The process of claim 1, wherein n is equal to 2 in formula (V) which is of general formula (IVc):



(IVc)

in which:

R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} are as previously defined and R_{13} and R_{14}, which are identical or different, independently are selected from a hydrogen atom, a C_{1-8} lower alkyl; a C_{6-12} aryl; a C_{7-12} arylalkyl; a C_{6-12} aryl substituted by a C_{1-5} alkyl; a C_{7-12} arylalkyl substituted by a C_{1-5} alkyl, with the proviso that R_7 and R_8 are different; and

At least one of C_1, C_2, C_3 and C_4 is an asymmetric carbon atom.

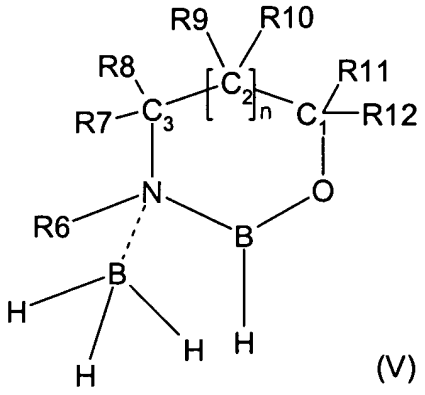
15. The process of claim 1, wherein the amount of compound of formula (IV) used in the reaction is ranging between 0.005 and 0.2 equivalent, based on the metal borohydride.

16. The process of claim 1, wherein the compound of formula (IV) is optically active α,α-diphenylpyrrolidin-2-yl-methanol.

17. The process of claim 1, used for the synthesis of chiral alcohols, comprising, further to the in situ preparation of the complex according to claim 23,

adding a ketone to be reduced.

18. The process of claim 17, wherein said complex is a chiral compound of general formula (V):

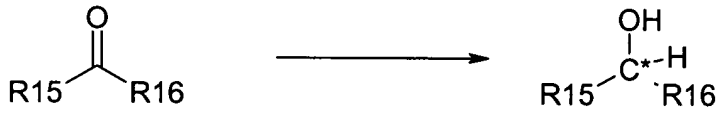


(V)

in which:

R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} and n are as defined in formula (IV) and at least one of C_1, C_2 and C_3 is an asymmetric carbon atom.

19. The process of claim 17, wherein said ketone is of general formula (VI) below and is reduced to an optically active alcohol of general formula (VII) below:



(VI) (VII)

in which R_{15} and R_{16} are different, are inert to reduction and are optionally substituted organic radicals which together can form a saturated or unsaturated ring.

20. The process of claim 19, wherein the asymmetric reduction of the compound of formula (VI) takes place under the following operating conditions:

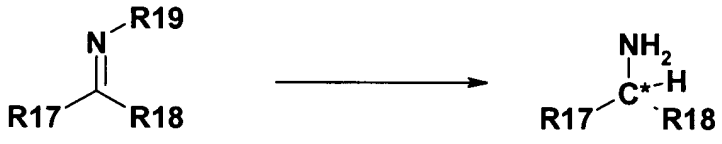
– adding the compound of formula (VI) slowly over a period of time ranging between 0.5 and 10 hours, under stirring;

– maitaining the temperature between 0°C and 75°C; and

– the amount of ketone is from 10 to 1000 times greater than that of the amino alcohol of formula (IV) used in the reaction.

21. The process of claim 19, wherein the compound of formula (VI) is 1-(2-thienyl)-3-chloropropanone and is added in an amount 50 to 100 times greater than that of the optically active compound α,α-diphenylpyrrolidin-2-ylmethanol.

22. The process of claim 18, comprising using the complex of formula (V), prepared in situ, to reduce the ether oxime of general formula (VIII) below to the corresponding optically active amine of general formula (IX):



(VIII) (IX)

in which:

R_{17} and R_{18} are different and the chirality of the secondary amine obtained is defined by the carbon atom carrying the amine group;

R_{17} and R_{18} are inert to reduction, are organic radicals independently substituted by which group and together can form a saturated or unsaturated ring; and

R_{19} is an alkoxy, an aryloxy or an arylalkoxy.

23. The process of claim 1, wherein the C_{1-8} lower alkyl group, is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl and pentyl; the C_{1-15} arylalkyl group is selected from the group consisting of benzyl, phenylethyl and methylbenzyl; the C_{1-15} arylalkyl group is substituted by a C_{1-5} alkyl selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, and pentyl; the C_{1-15} arylalkyl group is substituted by a C_{1-5} alkoxy selected from the group consisting of methoxy, ethoxy, propoxy, butoxy and pentoxy;

24. The process of claim 1, wherein said alkylene is selected from the group consisting of methylene, dimethylene, trimethylene, tetramethylene, penta-methylene, o-phenylenemethylene and o-phenylenedimethylene.

25. The process of claim 2, wherein the linear or cyclic ether is selected from tetrahydrofuran and tetrahydropyran; the secondary or tertiary amine is selected from N,N-dimethylamine, N,N-diethylamine, aniline, N,N-diethylaniline and N-ethyl-N-isopropylaniline; the linear or cyclic thioether is dimethyl sulfide; the amino ether is selected from morpholine; and a phosphine.